

# EDITORIALS

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## Of Job Actions and Such

THE RECENT air traffic controllers' strike somehow goes against the grain, much as do strikes and job actions by physicians, nurses or other health professionals when these occur. Perhaps this is because in both instances the health and safety of persons are put at risk by a relative minority for their personal gain, although the reasons are usually couched in euphemistic terms such as overwork or fatigue, or other reasons for inability to perform effectively in the public or patient interest. Leaving aside the issues of the legality of the air controllers' strike or their mass repudiation of a condition of employment they had each agreed to individually, this relatively small segment of the nation's population has sought to hold a much larger segment of the nation in economic hostage and to risk public safety in the air space to gain their special ends. Health professionals have not yet gone this far, although they are also essential when the health and safety of persons or the public are at risk, as in a hospital. And it is to their credit that health professionals have always made provision to maintain basic emergency care during their strikes and job actions, and by so doing have diluted the potential strength of their job actions.

Many things are changing as our society becomes more technologically complex, its people more technologically specialized, and the whole more technologically and therefore more economically interdependent. Specialization within this growing complexity has given rise to special interest groups which by definition must be minorities seeking to advance their own particular interests within the framework of the interdependent majority or whole. As complexity has continued to increase many such special interest groups have become more organized and more effective in advancing their cause. One can easily watch the growing importance and effectiveness of many of them in the political arena. Then, because interdependence increases along with specialization, each special interest group becomes a yet more essential cog in the machinery of the interdependent whole, with the result that its power, through strikes or job actions, to disrupt

and damage the interdependent whole also increases. And indeed there is evidence that this can be and has been increasingly hurtful in the competitive world in which we as a nation now find ourselves.

A real question is at what point does costly disruption, or real danger to the health and safety of persons or the public, become too counterproductive from the standpoint of the majority, or society as a whole? Can we any longer afford the hurt and cost of strikes and job actions for the special interest of minority groups against the majority or the interdependent whole? Could it be that this is a tool or process that is beginning to outlive its value to our society now that the world is becoming more complex and competitive? It would seem that there must be some more civilized way for special groups with special interests to make their need, if not their greed, known to the majority, and be treated fairly. Considering what lies ahead for medicine and health care, it may not be too soon for the health professions to seek some better and less disruptive alternative to traditional strikes and job actions, which also go so much against the grain, where the health and safety of the public are concerned.

—MSMW

## Classification of Malignant Lymphomas

ELSEWHERE IN THIS ISSUE is the Medical Progress article "Malignant Lymphomas: Cell Surface Markers and Advances in Classification" by Dr. James A. Strauchen.

The non-Hodgkin's lymphomas have been a source of confusion and controversy for both clinicians and pathologists for decades. The approach of Rappaport, published initially in the mid-1950's,<sup>1</sup> gave a spark of enlightenment, and it was appreciated finally in the early 1970's for helpful clinical correlation only after a lengthy period of gestation. Its major contribution was the demonstration that lymphomas exhibiting nodular

cellular proliferations were less aggressive and had longer median survival than those of the same cytologic type with diffuse histologic patterns.<sup>2</sup> The concept of Rappaport, however, did not relate the nodular proliferations of lymphoma cells to follicles but identified twice as many cases with a favorable prognosis as the follicular lymphoma.<sup>2,3</sup>

In the early 1970's Lukes and Collins presented a functional or immunologic approach to the malignant lymphomas, attempting to relate these disorders to the explosive developments in immunology of the 1960s.<sup>4</sup> Lymphomas were related to the T cell and B cell systems and lymphocyte transformation. A multiparameter technical approach, including immunologic surface marker studies, was presented for the redefinition of these disorders. A follicular center cell concept also was proposed by Lukes and Collins as a basis for their approach in which the follicular center was considered a site of B cell transformation.<sup>4,5</sup> According to this concept, the small B lymphocyte under antigenic stimulus evolved through cleaved cell stages to a noncleaved cell and eventually moved out of the follicular center as a B-immunoblast, the fully transformed B-lymphocyte and precursor of the plasma cell. Small and large cleaved cells were identified as the marker cells of normal follicular centers and the small and large noncleaved as the dividing cells of the follicular center.<sup>4,6</sup> Lymphomatous counterparts of each of these follicular center cells with varying frequency of follicle formation were identified and have distinctive clinical behavior and survivals.<sup>7,8</sup> It was proposed that nodular lymphomas were lymphomatous follicles composed of follicular center cells (FCC) with either cleaved or noncleaved FCC predominating.<sup>4</sup> At the time of the early publications of Lukes and Collins, before multiparameter studies, it was uncertain how many T cell and B cell subtypes ultimately would be identified. However, three predictions were made: (1) Lymphomas of large cells principally involved transformed lymphocytes of T cell and B cell types and, rarely, genuine histiocytes; (2) the nodular lymphomas of Rappaport were lymphomatous follicles composed of follicular center cells, and (3) lymphomas essentially were subtypes of the T cell and B cell systems. Our multiparameter studies from the intervening years have confirmed all of these predictions<sup>9-12</sup> as well as numerous investigators cited by Strauchen and summarized in a number of reviews.<sup>13-15</sup>

Initially, there were two strong candidates for

T cell subtypes, the cerebriform cell of mycosis fungoides and Sézary's syndrome and the convoluted lymphocytic lymphoma which was frequently associated with mediastinal masses, most commonly observed in teenagers and young adults who often developed acute lymphocytic leukemia (ALL).<sup>16</sup> The convoluted T cell lymphoma/leukemia, also known as lymphoblastic lymphoma,<sup>17</sup> has become a well-recognized and generally accepted entity that interrelates with T cell ALL. Two other subtypes seemed likely, the small lymphocyte of T cells (T cell CLL [chronic lymphocytic leukemia]) and T-immunoblastic sarcoma, both of which were subsequently confirmed and added to the classification of Lukes and Collins.<sup>10,11</sup> Finally, a fifth type, the lymphoepithelioid cell, which is the distinctive T cell lymphoma previously included in the heterogeneous group of disorders of the so-called Lennert lesion, has been established in the study of a small group of cases.<sup>11,18</sup>

Using a continually expanding variety of techniques, many of which Strauchen has discussed, including immunologic surface marker studies, cytochemistry, electron microscopy, immunoperoxidase, monoclonal antibodies, cell kinetics, numerous investigators, including ourselves, have established the malignant lymphomas as neoplasms of the immune system involving principally T cell and B cell types and rarely of histiocytes as macrophages. The lymphoma of large cells, previously known as reticulum cell sarcoma of histiocytic lymphoma, principally involves transformed lymphocytes of T cell and B cell types. The diffuse lymphomas of the past have been shown to be heterogeneous groups and included both T cell and B cell types which blurred clinical and morphologic distinctions. As a result of multiparameter studies, numerous clinical, morphologic and immunologic entities are emerging, possibly as many as 10 to 12 in all. Of great importance is the appreciation that malignant lymphomas are composed of cytologic types which are counterparts of normal cells and represent defective immune cells with varying degrees of abnormality. They, thus, migrate and home to the respective T cell and B cell sites and function, to varying degrees, like normal cells. Thus, as the entities are studied in detail, it is apparent that the initial presentation, distribution and frequency of tissue involvement reflect, to some extent, the normal counterparts of the lymphomatous cells.

Lymphomas develop, as Strauchen has indi-

cated, in the T cell and B cell lineage either at various levels of development or in the effector cells. Lymphomas of immunoblasts in the T cell and B cell systems represent the deviation from the developmental concept since they represent the dividing cell or the proliferative state of the effector cell rather than a precursor cell in the system as the term "immunoblast" might suggest. Thus, immunoblastic sarcoma of T cell or B cell type may be encountered either in the initial presentation as a highly aggressive process or in a late stage having evolved from a low grade or effector type cell, such as chronic lymphocytic leukemia of B cell type, when it changes to a large cell, the B immunoblast in the entity known as Richter's syndrome. We have observed immunoblastic sarcomas developing in many of the small subtypes of the T cell and B cell system. In addition, B-immunoblastic sarcoma develops, in our experience, in a wide variety of abnormal immune states, such as immunoblastic lymphadenopathy, Sjögren's syndrome and systemic lupus erythematosus (SLE)-like disorders.<sup>19</sup> Appreciation of the phenomenon of lymphocyte transformation thus has helped us understand that the appearance of a second cytologic type of lymphoma is most likely a change in the kinetic state, from low to high grade, rather than the occurrence of a genuinely different second type of lymphoma previously designated as a composite lymphoma. The occurrence of a second lymphoma, such as immunoblastic sarcoma in Hodgkin's disease, also may represent clonal evolution from the same defective clone (according to unpublished data ["Association of Hodgkin's Disease With Immunoblastic Sarcoma of B Cell Type: An Immunohistological Study"] by B. Falini, I. DeSolas, W. Fish and C. R. Taylor), but further studies are needed to clarify this issue.

The dramatic development of modern immunology since the 1960's has provided a sound basis for the understanding of the immune system and its neoplasms, the malignant lymphomas and related lymphoid leukemias. The immunologic investigations have put at our disposal a technical armamentarium for the redefinition of the cytologic types and permitted precise characterization. For the morphologist, these techniques have allowed greater insight and a new appreciation of the significance of the morphologic features, and permitted the recognition of the heterogeneity of the cytologic types of the past, such as histiocytic lymphoma and poorly differentiated lymphocytic

lymphoma of Rappaport, as well as childhood acute lymphocytic leukemia (ALL). Using multi-parameter studies, we have investigated over 800 cases of non-Hodgkin's lymphomas and related leukemias and discovered that the morphologic features in carefully collected and properly processed histologic material can be an effective predictor of the T cell and B cell subtypes by an experienced hematopathologist.<sup>12</sup> Numerous technical problems in the application of the multi-parameter procedures, together with biologic variations of lymphoma cells, render the effectiveness of the techniques far from perfect and inferior in our hands to the morphologic identification of cytologic types.<sup>10-12</sup> The use of the recently developed, highly specific monoclonal antibodies produced by the hybridoma system offers great promise in the future of elevating the lymphoma cell characterization to a high level of sophistication. Our experience with monoclonal antibodies on both cell suspensions and frozen sections thus far indicates that this approach is not free of problems, and it will be some time before both their precise role and effectiveness will be established.

The new formulation for pathology of malignant lymphomas, resulting from a study sponsored by the National Cancer Institute, discussed by Strauchen, is not intended as a new classification, but as a basis for translating the major classifications in use around the world. It is unfortunate that a consensus could not be achieved on an immunologic classification with T cell and B cell subtypes since this serious omission renders the formulation for pathology outmoded at the time of publication. It is, indeed, a remarkable and unparalleled study, and it is unfortunate that this final and most important step could not be achieved. Unquestionably, the new formulation will provide an improved understanding of the relationship of the various classifications and put to rest much of the controversy and debate. The clinicopathological correlation data, accumulated from the enormous statistical studies, provide extremely valuable information for comparison studies from medical centers around the world.

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## Malaria: A Great Relatively Neglected Disease

LAST YEAR in an address to an international meeting on malaria, I spoke about the "great neglected diseases of mankind"—diseases that are vast in number (hundreds of millions of cases at least) and neglected in terms of scientific interest and financing. I was not only informed, in a slightly offended tone of voice, that malaria is not a neglected disease, but I had to agree that it was in relatively good shape. For instance, it was one of the six chosen diseases of the Tropical Diseases Research Programme of the World Health Organization (WHO) and, among those, it is funded at two

to three times the level of any of the others. At present, this equals all of \$4 million a year. This is particularly poignant in view of the remark of a Trustee of the Rockefeller Foundation, Richard W. Lyman (now its President), when enthusiastically informed of the WHO Programme several years ago: "Perhaps we should call them the great relatively neglected diseases of mankind."

Total global support for research in all of these diseases is about \$60 million per annum. Compare this with cancer: with a prevalence of nearly 10 million cases worldwide, cancer research receives \$40 million from the American Cancer Society alone, plus another \$1,000 million a year from the National Institutes of Health. The National Institute of Allergy and Infectious Diseases' total budget for all parasitic infections, most of which are great neglected diseases, was about \$18 million this year.

Malaria is unquestionably a great disease—300 million cases annually, with 1 million childhood deaths in Africa alone. Many think it is the greatest single health scourge of mankind. Nevertheless, the huge global effort to eradicate malaria has been abandoned. In the words of the Director General of the World Health Organization, "we have thrown in the towel." An impossible dream had not been achieved. Immediately after World War II there were two exceedingly powerful new tools, DDT (a uniquely long-acting insecticide) and chloroquine (a nontoxic prophylactic and curative drug). The time appeared ripe for eradication and, in subsequent years, the accomplishment was great. But now mosquitoes in most endemic areas are resistant to DDT, and in entire regions such as Southeast Asia parasites are more than 80 percent resistant to chloroquine. Sulfadoxine pyrimethamine (Fansidar), another excellent new drug, now shows 20 percent resistance. Quinine is again in wide use.

The incredibly versatile malaria parasite is now undergoing a resurgence globally. Sri Lanka, a large island, had almost eradicated malaria, with about one recorded case per month. Twelve years ago, in a matter of months, the incidence of malaria increased to more than a half million cases and it remains at that annual level today. The vast land areas and populations of India are steadily being invaded by the mosquito and the parasite; from 100,000 cases annually in the early 1960's to 30 to 50 million today. Malaria has returned to Europe, causing epidemics in the rural areas of Western Turkey. It is another one of the many